Postnatal Intermittent Hypoxia and Developmental Programming of Hypertension in Spontaneously Hypertensive Rats

The Role of Reactive Oxygen Species and L-Ca$^{2+}$ Channels

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Abstract—Obstructive and central apneas during sleep are associated with chronic intermittent hypoxia (CIH) and increased cardiovascular morbidity. Spontaneously hypertensive rats exposed to CIH during postnatal days 4 to 30 develop exaggerated hypertension as adults. We hypothesized that reactive oxygen species and altered L-Ca$^{2+}$ channel activity may underlie the postnatal programming of exaggerated blood pressure and cardiac remodeling. Newborn male spontaneously hypertensive rats were exposed to CIH (10% and 21% O$_2$ alternating every 90 seconds, 12 h/d, for postnatal days 4 to 30) or normoxia (room air). In each condition, spontaneously hypertensive rats received daily (SC) 1 of 3 treatments: 1-calcium channel blocker nifedipine (5 mg/kg), superoxide dismutase mimetic MnTMPyP pentachloride (10 mg/kg), or vehicle (polyethylene glycol). Blood pressure was evaluated monthly for 6 months after birth, and echocardiographic assessments were conducted at 6 months of age. CIH vehicle-treated rats presented higher systolic blood pressure (187±5 mm Hg) as compared with normoxic vehicle treated controls (163±2 mm Hg; P<0.001). Postnatal CIH elicited marked increases in left ventricular wall thickness in a pattern of concentric hypertrophy with augmented systolic contractility. The treatment with nifedipine in the CIH group attenuated blood pressure (159±2 mm Hg; P<0.001) and normalized left ventricular wall thickness and systolic function, whereas the treatment with SOD mimetic decreased blood pressure (165±2 mm Hg; P<0.001) and reduced left ventricular wall thickness without changes in the systolic function. We conclude that Ca$^{2+}$ and reactive oxygen species–mediated signaling during intermittent hypoxia are critical mechanisms underlying postnatal programming of an increased severity of hypertension and hypertrophic cardiac remodeling in a genetically susceptible rodent model. (Hypertension. 2008;52:156-162.)

Key Words: intermittent hypoxia ■ calcium channels ■ oxidative stress ■ sleep apnea ■ hypertension

Intermittent hypoxia (IH) during sleep is one of the characteristics of sleep apnea that is associated with substantial cardiovascular (CV) morbidity, such as hypertension and heart failure. Sleep-disordered breathing with apneic episodes and intermittent hypoxemia are frequently encountered in young children; however, the potential consequences of postnatal IH on adult CV dysfunction are not clear. There is accumulating evidence that IH is associated with an increased oxidative stress$^{2-6}$ and that redox signaling during this condition has been extensively implicated in CV pathophysiology, including some forms of hypertension and cardiac function.$^{2,7-9}$ Perinatal l-arginine and antioxidant supplements were shown to reduce blood pressure (BP) in adult spontaneously hypertensive rats (SHRs), suggesting a critical role of oxidative status during perinatal development in programming BP later in life.$^{10}$ In previous work from our laboratory, we demonstrated that SHRs exposed for the first 30 days of postnatal life to a chronic intermittent hypoxia (CIH) regimen that mimics sleep apnea will develop much more severe hypertension as adults when compared with normoxic controls.$^{11}$ The long-term effects of CIH were most likely mediated by the interaction between genetic predisposition for hypertension, as seen in SHRs, and the persistent blunting of baroreflex functions, as elicited by CIH. Interestingly, normotensive Sprague-Dawley rats exposed to perinatal chronic IH for the same time frame will not develop elevated BPs as young adults, despite persistently blunted baroreceptor function. This may suggest activation of redundant mechanisms aiming to preserve normal BPs.$^{11,12}$

Previous studies have shown that SHRs experience oxidative stress because of enhanced production of reactive oxygen...
species (ROS) by increased reduced nicotinamide-adenine dinucleotide phosphate oxidase activity and also through dysfunctional endothelial NO synthase (uncoupled). Impaired endothelium-mediated vasodilation in hypertension has been linked to decreased NO synthesis or to increased NO degradation because of its interaction with O$_2$ to form ONOO$.^16$ ROS also lead to apoptosis of endothelial cells, loss of microvessels in SHR, and promote leukocyte adhesion to the endothelium resulting in further ROS release.\(^{18}\) Inhibition of ROS generation with apocynin (a reduced nicotinamide-adenine dinucleotide phosphate oxidase inhibitor) or allopurinol (a xanthine oxidase inhibitor) and radical scavenging with antioxidants or SOD mimetics decreased systemic BP and prevented development of hypertension in most animal models of hypertension. The beneficial effects of these antioxidant strategies have been attributed to the following: (1) normalization of endothelial function, (2) regression of vascular remodeling, (3) reduced vascular inflammation, and (4) improved renal function.\(^{15}\)

One of the first and early responses to hypoxia in various cell types is an increase in intracellular Ca$^{2+}$ ([Ca$^{2+}$]i) that could be implicated in ROS-mediated CV effects. ROS increase the cytosolic Ca$^{2+}$ level through mobilization of intracellular Ca$^{2+}$ stores and/or through the influx of extracellular Ca$^{2+}$.$^{19–22}$ A direct modulation of Ca$^{2+}$ channels by ROS and ROS-dependent increases in vascular intracellular Ca$^{2+}$ primarily via extracellular Ca$^{2+}$ influx have been conclusively demonstrated.$^{19,23,24}$ In cardiac and vascular tissues, 2 types of Ca$^{2+}$ channels (L- and T-type) are present,$^{25}$ and high voltage-gated L-Ca$^{2+}$ channels play a critical role in excitation-contraction coupling in cardiac, skeletal, and smooth muscle tissue.

We examined the hypothesis that ROS and L-Ca$^{2+}$ channels are involved in long-term alterations of CV function observed in adult SHRs after postnatal exposures to CIH. We, therefore, evaluated the protective roles of antioxidant treatment with the superoxide dismutase mimetic MnTMPyP pentachloride and with the L-type Ca$^{2+}$ channel blocker nifedipine in preventing the more severe hypertensive phenotype and cardiac remodeling induced by postnatal CIH in SHRs.

**Materials and Methods**

All of the experimental protocols were approved by the University of Louisville Institutional Animal Use and Care Committee and were in accordance with National Institutes of Health requirements for the care and use of laboratory animals.

**Experimental Groups**

Pregnant SHRs were purchased from Charles River Laboratories (Wilmington, MA). Litters were randomly assigned into 1 of 6 groups. Rats of the first 3 groups were exposed to chronic IH as described previously.$^{11,12}$ from postnatal days 4 to 30 (pups exposed at day 1 had a poor survival rate). During this time they received daily SC injections of the following: (1) ROS scavenger SOD mimetic MnTMPyP pentachloride (manganese [III] tetrakis [1-methyl-4-pyridyl] porphyrin pentachloride; 10 mg/kg per day; Alexis Biochemical Corp); (2) L-type Ca$^{2+}$ channel blocker nifedipine (5 mg/kg per day in 0.02 mL of polyethylene glycol 400; Sigma); (3) vehicle (polyethylene glycol and polyethylene glycol 400, 0.02 mL/d; Sigma). Three other groups of SHRs received similar treatments but were exposed to room air (RA) as normoxic controls. Accordingly, the groups were labeled as IH/RA-SODm, IH/RA-Nif, and IH/RA.

**Lipid Peroxidation**

Total lipid peroxides were measured as the sum of malonaldehyde and 4-hydroxyalkenals using a commercially available kit (Biosys LPO-586; Oxisresearch, OXIS International, Inc) using cardiac tissue homogenates from rat pups exposed to IH from day 4 for 2 weeks and treated with either vehicle or the SOD mimetic. Protein concentration was determined using a Protein Assay kit (Bio-Rad Laboratories).

**BP Measurements**

Automated occlusion plethysmography (tail cuff method) was used and involved an analog-to-digital signal converter and a digital acquisition and analysis system (Kent Scientific Corp), as recommended. At least 8 to 10 BP readings were obtained from each rat; these values were then averaged to yield the mean BP for that time point for each rat. Systolic and diastolic pressure and heart rate were measured every 4 weeks, starting at week 4 of postnatal life through week 24.

**Echocardiographic Assessment of LV Function**

M-mode, 2D, and spectral Doppler echocardiography were performed as described previously.$^{26,27}$ Imaging was performed under light anesthesia with ketamine (22 mg/kg, IM) and xylazine (2.7 mg/kg, IM), using a Toshiba 380 PowerVision machine and a pediatric broad-band transducer operating at 10-MHz frequency and 120-Hz frame rate. At the age of 6 to 7 months, the following variables were measured: LV end-diastolic and end-systolic diameter (LVEDD and LVESD), anterior wall thickness (AWT) and posterior wall thickness (PWT) at end diastole, and ejection time from the aortic Doppler trace. LV hypertrophy was indexed by relative wall thickness at end diastole (RWT = [LVEDD + 2 x PWT]/LVEDD) and LV systolic function by fractional shortening (FS = [LVEDD – LVESD]/LVEDD) and the mean velocity of circumferential fiber shortening (V$_{ef}$ = FS/ejection time).

**Data Analysis**

Data were tabulated, and responses were compared using 1- or 2-way ANOVA or Student t tests, followed by Newman-Keuls posthoc tests. A $P<0.05$ was considered to achieve statistical significance. The results are expressed as means±SEMs.

**Results**

**Body Weight**

Body weights were significantly reduced among 6-month–old IH-exposed rats compared with corresponding RA controls receiving vehicle, SOD mimetic, or nifedipine (by 13.6%, 13.3%, and 14.6%, respectively; $P<0.001$). There were no differences between the weights of IH-vehicle SHR and those of IH-exposed rats receiving SOD mimetic or nifedipine treatment (Figure 1).

**Lipid Peroxide Measurements**

In 6 rat pups treated from day 5 of life with IH and SOD mimetic, cardiac lipid peroxide levels were 376±34 μmol/L per milligram of protein compared with 895±43 μmol/L per milligram of protein in 5 rat pups treated with IH and vehicle ($P<0.05$).
Temporal changes in blood pressure over 6 months in 6 groups of SHRs exposed to either normoxia (RA) or IH from day 4 to day 30 of life and receiving vehicle, the SOD mimetic MnTMPyP pentachloride (10 mg/kg per day), or nifedipine (5 mg/kg per day). IH indicates treated with vehicle (polyethylene glycol 400, 0.02 mL/d); IH-SODm, IH rats receiving SOD mimetic; IH-Nif, IH rats receiving injections of nifedipine; RA, rats raised in RA receiving vehicle similar to IH rats; RA-SODm, RA rats receiving SOD mimetic similar to IH rats; RA-Nif, RA rats receiving nifedipine similar to IH rats. Data are shown as means±SEMs. Data show the significant differences in the corresponding baseline (RA groups receiving similar treatment).

Changes in BP and Heart Rate
Eight male SHRs completed the experimental protocol for each of the 6 treatment groups. BP measurements at ages 1 and 6 months are summarized in Figure 2. By 6 months of age, IH-exposed SHRs developed significantly higher systolic and diastolic pressures than RA SHRs (187±5 and 163±2 mm Hg, P<0.001; and 139±6 and 87±3 mm Hg, P<0.01, respectively). Treatment of IH-exposed rats with the SOD mimetic MnTMPyP pentachloride or with the L-Ca2+ channel blocker nifedipine abrogated the IH-induced BP increases (Figure 2A and 2B), such that both systolic and diastolic BPs were similar to corresponding treatment RA-exposed controls. There were no differences in either systolic or diastolic BPs among the 3 groups of RA-exposed rats (P>0.05; Figure 2A and 2B). No differences in HR occurred at 6 months of age among all of the experimental groups (Figure 2C).

Echocardiographic Examination of LV Function
Representative LV M-mode echocardiograms from each experimental group are shown in Figure 3. Cardiac structure and function were significantly affected in IH-exposed SHRs as compared with RA vehicle controls. The phenotype observed was that of concentric LV hypertrophy, with IH-exposed animals exhibiting smaller LV chamber size (decreased LVEDD and LVESD; P<0.001; Figure 4), increased wall thickness (AWT, PWT, and RWT; P<0.05; Figure 4), and augmented systolic function (FS, P<0.001, and Vcf, P<0.05; Figure 4) in IH vehicle-treated rats compared with normoxic rats.

Treatment with nifedipine (Table and Figure 4) significantly attenuated IH-induced concentric hypertrophy resulting in smaller RWT (P<0.05 versus IH vehicle; P value not significant versus RA nifedipine), increased LV chamber size (LVESD, P<0.05 versus IH-vehicle; P value not significant versus RA nifedipine), and normalization of systolic function (Vcf, P<0.001 versus IH vehicle; P value not significant versus RA nifedipine). Moreover, although the effects were not as uniformly striking, treatment with an SOD mimetic also resulted in similar responses, with smaller increases in RWT (P<0.05) and strong trends toward normalization of both systolic function (FS, P=0.054, and Vcf, P=0.095) and LV chamber size (LVESD, P=0.073) as compared with IH vehicle–exposed rats.

Discussion
This study shows the critical role of ROS and L-Ca2+ channels in the plasticity of BP control mechanisms as induced by IH exposures during the early postnatal period. Indeed, whereas nonhypertensive rat strains, such as Sprague-Dawley rats, display lifelong alterations in baroreflex, genetically hypertensive rats, such as SHRs, will manifest markedly higher BP compared with normoxic controls when subjected to IH postnatally. Thus, treatment of neonatal SHR male pups with either the SOD mimetic MnTMPyP pentachloride or with the L-Ca2+ channel blocker nifedipine prevented the exaggerated increases in BP and, to varying degrees, attenuated long-term concentric hypertrophic LV
remodeling. In SHR-IH, the developmental changes in BP were accelerated with the prehypertensive period composed of 2 months versus 3 months in other groups (Figure 2A and 2B). The more severe hypertension and LV remodeling in the CIH-vehicle group at 6 months could be ascribed because of a variety of mechanisms initiated by exposure to CIH.4,11,12,17,26,27 ROS and L-Ca²⁺ channel mechanisms might not necessarily be the only standing mechanisms for the exaggerated CV dysfunction at 6 months in the SHR, although they appear to be critical for the initiation and progression of the developmental programming of long-term CV morbidity after CIH in neonatal SHRs.

**Body Weight**

All of the IH-exposed rats, both those receiving vehicle as well as those receiving treatment, had lower body weights at 6 months of age compared with corresponding RA-exposed rats. Because the duration of IH was only during the first month of postnatal life, one might have predicted catch-up growth in the subsequent 5 months of normoxia. Epidemio-
logical studies indicate that the low birth weight or alternatively the accelerated somatic growth that occurs after birth are major determinants in the risk for developing hypertension in adulthood.28–30 However, such were not the growth characteristics of the animals included in our experiments. In fact, SHR exposed to IH had the same birth weight as those slated to RA exposures, and, as mentioned, IH-exposed SHR did not sustain periods of marked accelerated growth after discontinuation of IH. Therefore, it is very unlikely that factors such as birth weight or somatic growth patterns may account for the disparities in BP temporal trajectories in IH-vehicle SHR. CIH in SHR may reduce nutrient intake. In addition to low weight gain, protein deficiency could cause impairment in the redox status, decrease antioxidant defense mechanisms, and increase markers of oxidative stress.31,32 Antioxidant therapy was shown to normalize adult hypertension, vascular dysfunction, microvascular rarefaction,10,33 and LV hypertrophy34 associated with in utero exposure to a low-protein diet.

Blood Pressure

The perinatal period is a critical stage in development, whereby perturbations such as IH can lead to lifelong alterations in organ structure and function, a phenomenon that has been termed “metaplasticity.”15,36 For example, postnatal hyperoxia and either prenatal or postnatal IH induce lifelong modification of respiratory control networks.37,38 Analogous to such findings, we have reported previously on the anatomic and functional changes in baroreceptor-related networks in Sprague-Dawley rats after early postnatal IH.12 Interestingly, prenatal IH was not associated with such alterations.12 Furthermore, in this normotensive rodent strain, the persistent modification of baroreflex functions was not accompanied by changes in BP. Considering the postnatal IH-induced potentiation of the underlying systemic hypertension in the SHR model as found in the current experiments, we assume that redundant mechanisms aiming to preserve the normotensive status may have been effectively operational in the IH-exposed Sprague-Dawley rats.39 However, in a genetically predisposed hypertensive animal model such as the SHR, those mechanisms will be either ineffective or already fully activated, such that any additional “prohypertensive burden,” such as that induced by postnatal IH, will entail an increment in the severity of the underlying hypertension.

Therefore, the changes in BP and cardiac function after postnatal IH could result not only from intracellular but also from extracellular neural and humoral mechanisms that control the heart. In our preceding studies, we found increased sympathetic chemoreflexes, decreased baroreflex control of HR and sympathetic activity, and decreased heart rate variability in normotensive Sprague-Dawley rats subjected to the same IH protocol.11,12,40 We and others have also shown that IH induces oxidative stress, which induces apoptotic cell losses within the central nervous system in adult and newborn animals, including CV control nuclei.3,5,6,41–43 Interestingly, when adult rats are exposed to an IH protocol, LV dysfunction occurs and appears to be mediated, at least in part, by increased oxidative stress.2 Perinatal IH exposures are also associated with plasticity and metaplasticity of neural responses, more specifically as they are related to chemoreceptor, sympathetic, and somatic nerves, all of which may reflect the principal mechanisms underlying the long-term changes in CV control.44–46

It is now well established that increases in BP are determined by corresponding increases in peripheral vascular resistance. In the present study, BP returned to control levels when IH-exposed SHR received an SOD mimetic, further confirming the role of ROS in the IH-induced exacerbation of BP elevation in SHR. It is likely that scavenging of the excessive production of ROS associated with IH may have prevented ROS-related suppression of vasodilation because of decreasing NO availability in endothelial cells and formation of toxic ONOO−.16 Of note, endothelial NO synthase is extensively present at birth with a distribution similar to the pattern found in mature animals,47 and such processes are altered in SHR with reduced bioavailability of uncoupled NO synthase.15 The role of Ca2+ channels in vascular dysfunction is not only supported by the beneficial responses to nifedipine in our experiments but is also supported by the fact that ROS can modulate the permeability of Ca2+ channels in the vascular smooth muscle cells and in the myocardium.19,23

**LV Function**

Vehicle-treated IH SHR exhibited concentric LV hypertrophy and augmented systolic function that paralleled the
exaggerated hypertensive response. These structural changes most likely reflected the effects of chronically increased afterload on the heart and compensatory LV hypertrophy. Recent evidence from human studies shows that normotensive patients with obstructive sleep apnea (OSA) present an increase of LV mass of similar magnitude to patients with hypertension but no OSA and that both conditions operate in an additive fashion. Similar findings were reported for LV wall thickness. The increased ventricular afterload was correlated with increased large arterial stiffness and heart remodeling in both OSA and hypertension.

Although blockade of L-type calcium channels with nifedipine and amelioration of oxidative stress with an SOD mimetic both prevented the IH-induced rise in BP and, thus, reduced afterload equally, nifedipine imparted a much greater effect in attenuating the concentric remodeling phenotype. There is a possibility of an interplay between the effects of nifedipine and SOD. SOD increases the bioavailability of NO to dilate resistance vessels; however, NO-mediated vasodilator responses in SHRs were markedly diminished after the blockade of Ca\textsuperscript{2+} channels with nifedipine. This could suggest that NO dilates arteries via direct and/or hyperpolarization-induced closure of L-Ca\textsuperscript{2+} channels. Also, nifedipine increases NO bioavailability by antioxidative mechanisms and by upregulating SOD expression in endothelial and vascular smooth muscle cells. In our experiments, both SOD mimetic and nifedipine decreased BP, although only nifedipine decreased systolic function. This may suggest that SOD mostly affected peripheral vascular resistance, whereas nifedipine affected both vascular resistance and heart contractility. These observations indicate that, in addition to IH-mediated hypertension and the indirect effects of augmented load on the heart, IH may also induce direct myocardial effects related to L-type calcium channel function that contribute to long-term LV remodeling. Indeed, because nifedipine appeared more efficient than the SOD mimetic in preventing pathological LV remodeling, L-type Ca\textsuperscript{2+} channels may potentially represent a target for ROS in the neonatal myocardium, and in the context of oxidative stress, some degree of irreversibility may occur. It is also possible that the higher doses of the SOD mimetic may be needed for more complete protection of cardiac structure and function, and over and above the levels required for lowering BP and for recovery of the vascular response. In agreement with our results, transfer of human extracellular SOD gene into SHRs did not reduce cardiac output, such that the reduction of systemic BP in SHRs is likely the result of a decrease in systemic vascular resistance.

Limitations of the Study

Although IH is a hallmark of OSA, our model do not replicate all of the OSA-related features, which also include hypercapnia, sleep fragmentation, and reduced sleep hours. However, the latter features of OSA are more likely to occur at later ages, and IH is by far the most common perturbation in young infants suffering from apnea of prematurity. An additional limitation would have been the desirable inclusion of a combined SOD mimetic and nifedipine group, which would allow for examination of the relative contributions of each of the putative separate mechanisms potentially underlying the potentiation of the CV phenotype after postnatal chronic IH.

Perspectives

Postnatal IH, as might occur in premature infants, not only induces long-lasting alterations of baroreflex circuitry but is further associated with aggravated systemic hypertension in genetically predisposed animals. We propose that interactions between genetic susceptibility to hypertension, as in SHRs, and mechanisms that disrupt baroreceptor function and elicit increased oxidative stress, such as postnatal IH, could provide realistically possible clinical settings for the perinatal programming of CV pathology in adults and their altered phenotypic expression. Early intervention during postnatal ontogenesis using traditional antihypertensive drugs, such as nifedipine or a SOD mimetic, effectively prevented the incremental hypertensive effects of neonatal IH and, therefore, suggests potential therapeutic measures. However, additional studies will be required for delineation of the exact mechanisms within the vascular bed and the myocardium that underlie the long-term cardiac remodeling induced by postnatal IH.

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Disclosures

None.

References

12. Soukhova-O’Hare GK, Cheng Z, Roberts AM, Gozal D. Postnatal inter-
mittent hypoxia alters baroreflex function in adult rats. *Am J Physiol
ion formation in vascular tissues from spontaneously hypertensive and desox-
Suematsu M, Zweifach BW, Schmid-Schönbein GW. Xanthine oxidase
associated with arterial blood pressure in spontaneously hypertensive rats.
15. Touyz RM. Reactive oxygen species, vascular oxidative stress, and redox
Endothelial dysfunction in chronic myocardial infarction despite increase
vascular endothelial nitric oxide synthase and soluble guanilic cyclase
promotes endothelial cells apoptosis and loss of microvessels in the
25:2114–2121.
18. Marui N, Offermann MK, Sverlick R, Kunsch C, Rosen CA, Ahmad M,
Alexander RW, Medford RM. Vascular cell adhesion molecule-1
(VCAM-1) gene transcription and expression are regulated through an
antioxidant-sensitive mechanism in human vascular endothelial cells.
19. Tabet F, Savoia C, Schiffrin EL, Touyz RM. Differential calcium regu-
lation by hydrogen peroxide and superoxide in vascular smooth muscle
22. Perez-Reyes E. Molecular physiology of low-voltage-activated T-type
*Naunyn Schmiedebergs Arch Pharmacol*. 1999;360:646–653.
Gene expression of interleukin-6 in rat vascular smooth muscle during
287:R551–R559.
25. Morris L, Gozal D, Rosen CA, Ahmad M, Iwatsuki K, Varela S, Neustadt C,
Altura BM. Mechanisms of intermittent hypoxia associated with arterial blood pressure in spontane-
26. Marui N, Offermann MK, Swerlick R, Kunsch C, Rosen CA, Ahmad M,
Alexander RW, Medford RM. Vascular cell adhesion molecule-1
(VCAM-1) gene transcription and expression are regulated through an
antioxidant-sensitive mechanism in human vascular endothelial cells.
29. Perez-Reyes E. Molecular physiology of low-voltage-activated T-type
*Naunyn Schmiedebergs Arch Pharmacol*. 1999;360:646–653.
31. Ermak G, Davies KJ. Calcium and oxidative stress: from cell signaling to
32. Perez-Reyes E. Molecular physiology of low-voltage-activated T-type
33. Prabhu SD, ChandraSekar B, Murray DR, Freeman GL. β-Adrenergic
blockade in developing heart failure: effects on myocardial inflammatory
cytokines, nitric oxide, and remodeling. *Circulation*. 2000;101:
2103–2109.
35. Ashton N. Perinatal development and adult blood pressure. *Braz J Med
36. Law CM, Shiell AW. Is blood pressure inversely related to birth weight?
37. Law CM, Shiell AW, Newsome CA, Syddall HE, Shinsboure EA,
Fayers PM, Martin CN, de Swiet M. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of
38. Huang CJB, Fwu ML. Degree of protein deficiency affects the extent of the
depression of the antioxidative enzyme activities and enhancement of
39. Li J, Wang H, Stoner GD, Bray TM. Dietary supplementation with
cysteine prodrugs selectively restores tissue glutathione levels and redox
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